REMARKS

Reconsideration and allowance are respectfully requested.

The Examiner's indication that the Rule 181 Petition will be decided after issuance of an Action on the merits is, with due respect, inappropriate as the Examiner has issued an action on the merits before the applicants have received a review of the Examiner's restriction requirement by the Commissioner. While the claims have been amended to delete the non-elected subject matter the applicants believe the applicants should be afforded the opportunity to add the cancelled subject matter back in to the pending claims prior to a further Action on the merits yet after a Decision on the applicants' Rule 181 Petition. As the Commissioner may redefine the subject matter to be examined in this application, the Examiner's issuance of the Office Action of November 6, 2002, was, with due respect, submitted to be premature. A Decision on the applicants Petition prior to the issuance of a further Action on the merits is requested. The Office is requested to mail the Decision and, if favorable to the applicants, allow the applicants the opportunity to further amend the claims to include previously non-elected, withdrawn subject matter which may have been cancelled above, prior to issuance of a further Action on the merits.

The claims have been amended and the following remarks are submitted to advance prosecution and to be responsive. While the applicants acknowledge the Examiner's comment regarding the possibility of amending the claims to recite only the elected species (see paragraphs 7 and 8 of Paper No. 13), the applicants submit that

since claims 1, 34 and 47 are allowable generic claims, consideration of the additional species is appropriate. See, page 3 of Paper No. 8.

Claims 1, 3-5, 7-10 and 27-58 are pending. Claims 2, 6 and 11-26 have been cancelled, without prejudice. New claims 28-58 have been added. The amendments and new claims are supported by the original disclosure and, thus, no new matter has been added.

Claim 1 has been combined with the details of now-cancelled claims 2, 6, 11 and 12. Claim 1 provides to a process for preparing a pharmaceutical composition. New claim 28 specifies that the mutant herpes simplex virus comprises a heterologous gene and new claims 29 to 31 further define the heterologous gene. Basis for new claims 28 to 31 may be found, for example, in the specification at page 10 lines 15 to 19, page 11 lines 5 to 6 and page 13 line 23. Claims 32-33 specify that the additional nucleic acid sequences may encode ICP27 in addition to ICP4 and that the ICP27 gene may be driven by the ICP27 promoter. Independent claim 34 and dependent claims 35 to 46 are directed to a process for propagating a mutant herpes simplex virus vector comprising a heterologous gene. Basis for these claims can be found, for example, at page 10 lines 15 to 19, page 11 lines 5 to 6 and page 13 line 23. New independent claim 47 and dependent claims 48-58 are directed to a process for propagating a mutant herpes simplex virus using a cell line comprising a nucleic acid sequence encoding a functional equine herpes virus 1 gene 12.

The amendments are being made solely to advance prosecution of this application to allowance and do not constitute an acquiescence, abandonment or

disclaimer with respect to any subject matter originally claimed. Applicants reserve the right to pursue any excluded subject matter by way of one or more further application.

To the extent not obviated by the above amendments, the Section 112, second paragraph, rejection of Claims 1-12 and 27 is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following comments.

Claim 1 specifies that the mutation in the HSV VP16 gene is a mutation which reduces or abolishes the ability of the protein encoded by the VP16 gene to activate viral transcription without disrupting the structural activity of the protein. Basis for the recitation may be found, for example, at page 7, lines 2 to 10, of the specification.

Claim 1 refers to a nucleic acid sequence from a non-HSV herpes virus encoding a functional equivalent of the HSV VP16 polypeptide. Basis for this recitation can be found, for example, at page 14 line 29 to page 15 line 15 of the specification.

Claim 1 further specifies that "the nucleic acid sequence (i) complements the endogenous gene and (ii) does not undergo homologous recombination with the endogenous gene". Which the applicants submit will be clear and definite to one of ordinary skill in the art.

Withdrawal of the Section 112, second paragraph, rejection of claims 1-12 and 27 is requested.

The Section 112, first paragraph, rejection of Claims 1-12 and 27 is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following comments.

The Examiner has asserted that the specification "does not reasonably provide enablement for having a method for propagating a mutant HSV with any or all kinds of

VP16 gene mutations plus any one or more other additional endogenous gene mutations in the cell line transfected with any or all homology of VP16 of HSV". The Examiner has acknowledged that the specification is enabling for a method of propagating a mutated herpes simplex virus in1814 in a cell line comprising the full length equine herpes virus gene 12.

The in1814 herpes simplex virus comprises a mutation in its endogenous VP16 gene which reduces or abolishes the ability of the protein encoded by the VP16 gene to activate viral transcription without disrupting the structural activity of the protein. Other mutations of the HSV VP16 gene which reduce or abolish the ability of the protein encoded by the VP16 gene to activate viral transcription without disrupting the structural activity of the protein are known in the art (see page 7 lines 16 to 18 of the specification).

The EHV gene 12 is a functional equivalent of the HSV VP16 gene. EHV gene 12 encodes a protein which activates gene expression from immediate early gene promoters in both the EHV genome and the HSV genome. Thus, EHV gene 12 is functionally equivalent to wild-type HSV VP16 in that it trans-activates HSV immediate early (IE) gene expression. Functional equivalents of the HSV VP16 gene from non-HSV herpes viruses other than EHV are also known in the art to be capable of trans-activating HSV IE gene expression. See, for example, Moriuchi *et al* (Abstract lines 6 to 8). The manner by which immediate early gene expression is activated is thus known to be highly conserved in different herpes viruses and, consequently, one of ordinary skill in the art would reasonably expect the functional equivalents of HSV VP16 in all herpes viruses to activate HSV IE gene promoters.

Therefore, given both that mutations of the VP16 gene having the same effect as the in1814 mutation are known in the art and functional equivalents of VP16 in non-HSV herpes viruses are known in the art to trans-activate HSV IE gene expression, one ordinarily skilled in the art would be able to make and use the invention to propagate any mutant herpes simplex virus having a mutation in its VP16 gene which affects trans-activation activity but not structural activity using any cell line expressing a functional equivalent of HSV VP16 from a non-HSV herpes virus to provide the necessary trans-activation activity.

Withdrawal of the Section 112, first paragraph, enablement rejection of claims 1-12 and 27 is requested.

The Section 102 rejection of Claims 1-2, 5-6, 7 and 11 over Ace *et al.* is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following distinguishing comments.

Ace *et al* describes a method of growing the HSV mutant in1814 in a cell line that is transfected to express vmw110. Vmw110 is an immediate early gene which is transcribed as a result of the transcriptional-activation activity of the VP16 protein (see Ace *et al*, page 2260, left column, line 8). Vmw110 is not a functional equivalent of the HSV VP16 gene. Therefore, the claimed invention is novel over Ace *et al.*

The Section 102 rejection of Claims 1-2, 5-6, 7 and 11 over Moriuchi *et al.* is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following distinguishing remarks.

Claim 1 is directed to a process for preparing a pharmaceutical composition comprising the step of formulating the mutant HSV with a pharmaceutically acceptable

carrier or diluent. This step is not taught or suggested by Moriuchi *et al.* Moriuchi *et al* is concerned only with elucidating the function of the VZV ORF10 gene. Accordingly, claim 1 is novel over Moriuchi *et al.* as the reference fails to teach each element of the claims.

New claim 34 is directed to a process for propagating a mutant herpes simplex virus vector comprising a heterologous gene operably linked to a control sequence permitting expression of the heterologous gene in a mammalian cell. The in1814 virus of Moriuchi *et al* is not a viral vector and does not comprise a heterologous gene. The in1814 virus is an experimental tool and Moriuchi *et al* is not at all concerned with gene delivery using viral vectors. Accordingly, new claim 34 is novel over Moriuchi *et al.*

New claim 47 is directed to a process in which the complementing cell line comprises EHV1 gene 12. The cell line in Moriuchi *et al* does not comprise EHV gene 12. Accordingly, claim 47 is not anticipated by Moriuchi *et al.*

The Section 102 rejection of Claims 1-2, 5-6, 7 and 11 over Weinheimer *et al.* is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following distinguishing remarks.

Applicant respectfully disagrees with the Examiner that Weinheimer *et al* teaches a method for growing the herpes simplex virus mutant in1814. The only point at which Weinheimer *et al* mentions in1814 is in the introduction at the last paragraph at page 258. Here it is indicated that VP16 containing host cells were generated so that investigation of VP16 did not need to be limited to non-lethal mutations of VP16, such as in1814. Weinheimer *et al* does not describe the propagation of the in1814 mutant or any other HSV mutant having a mutation that selectively disrupts the trans-activation

activity but not the structural activity of VP16 using a cell line expressing the HSV-1 VP16 gene. Neither does Weinheimer *et al* describe the propagation of a mutant HSV using a cell line expressing a functional-equivalent of HSV VP16 gene from a non-HSV homologue. Therefore, the claimed invention is novel over Weinheimer *et al.*

The Section 102 rejection of Claims 1-2, 5-6, 7-9 and 11 over Johnson *et al.* is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following distinguishing remarks.

Johnson *et al* describes the growth of an HSV-1 virus with a mutated VP16 gene on a cell line containing wild-type HSV-1 VP16 gene, the aim being to achieve homologous recombination between the wild-type gene in the cell line and the mutated VP16 gene in the virus (page 6350 lines 7-44). This is the complete opposite to the claimed invention which uses a cell line containing a functional equivalent of the HSV VP16 gene from a non-HSV herpes virus to prevent homologous recombination occurring between the gene in the cell line and mutated VP16 gene in the virus. Therefore, the claimed invention is not anticipated by Johnson *et al.*

The Section 103 rejection of Claims 1-12 and 27 over DeLuca (WO 98/15637A1) in view of Elliott *et al.* is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following distinguishing remarks.

DeLuca does not disclose a method of making a mutated HSV with ICP4 and VP16 mutations. DeLuca describes a method of making a mutated HSV which has an ICP4 mutation and a mutation in the VP16-Oct1 consensus sequence TAATGARAT. This is the promoter sequence to which the VP16 protein binds in order to trans-activate

immediate early gene expression. The VP16 gene in the mutant HSV disclosed in DeLuca is not mutated (page 8 lines 10-22 and page 9 lines 24-27).

DeLuca teaches a method for complementing the defective HSV ICP4 gene using a cell line expressing HSV ICP4 and teaches that in order to reduce the probability of rescuing wild-type revertant virus when the cell line is used to grow the virus, the viruses should "include as little as possible non-coding HSV sequence $\tilde{3}$ and $\tilde{5}$ of the coding sequence in order to avoid introducing homologous sequences into the cell line". DeLuca does not teach that the HSV ICP4 gene can be complemented with anything other than the HSV ICP4 gene.

DeLuca also does not teach or suggest a method for complementing the VP16 gene. Since the sequence of the IE gene promoter to which the VP16 protein binds is mutated in the viruses of DeLuca, the skilled person would not be motivated to express HSV VP16 or any other gene having IE trans-activating activity, such as EHV-1 gene 12, in the complementing cell line. The virus described in DeLuca expresses a functional VP16 protein but this protein is unable to trans-activate IE gene expression because it is unable to bind to the IE gene promoter. Similarly, any VP16 protein expressed in the complementing cell line would be unable to trans-activate IE gene expression because it would be unable to bind to the IE gene promoter. The same applies to other proteins that are functionally equivalent to the HSV VP16 protein. Accordingly, the presently claimed invention would not have been obvious over DeLuca in view of Elliott *et al.* Withdrawal of the Section 103 rejection is requested.

Having fully responded to all of the pending rejections and objections contained in the Office Action, applicants submit that the claims are in condition for allowance and

earnestly solicit an early Notice to that effect. The Examiner is requested to contact the undersigned in the event anything further is required in this regard.

Return of an initialled copy of the attached PTO 1449 Form, pursuant to MPEP § 609 is requested.

Respectfully submitted,

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